



# Drug-induced psychosis: how to avoid star gazing in schizophrenia research by looking at more obvious sources of light

Alessandra Paparelli\*, Marta Di Forti, Paul D. Morrison and Robin M. Murray

Division of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK

## Edited by:

Andreas Meyer-Lindenberg, Central Institute of Mental Health, Germany

## Reviewed by:

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Joshua W. Buckholz, Vanderbilt University, USA

Markus Leweke, Central Institute of Mental Health, Germany

## \*Correspondence:

Alessandra Paparelli,  
Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK.

e-mail: [alessandra.a.paparelli@kcl.ac.uk](mailto:alessandra.a.paparelli@kcl.ac.uk)

The prevalent view today is that schizophrenia is a syndrome rather than a specific disease. Liability to schizophrenia is highly heritable. It appears that multiple genetic and environmental factors operate together to push individuals over a threshold into expressing the characteristic clinical picture. One environmental factor which has been curiously neglected is the evidence that certain drugs can induce schizophrenia-like psychosis. In the last 60 years, improved understanding of the relationship between drug abuse and psychosis has contributed substantially to our modern view of the disorder suggesting that liability to psychosis in general, and to schizophrenia in particular, is distributed through the general population in a similar continuous way to liability to medical disorders such as hypertension and diabetes. In this review we examine the main hypotheses resulting from the link observed between the most common psychotomimetic drugs (lysergic acid diethylamide, amphetamines, cannabis, phencyclidine) and schizophrenia.

**Keywords:** LSD, schizophrenia, amphetamines, psychosis, cannabis, PCP

The prevalent view among researchers today is that schizophrenia is a syndrome rather than a specific disease. Liability to this syndrome is highly heritable but the fact that concordance between monozygotic twins is less than 50% suggests an important role for environmental influences (Tandon et al., 2008; MacDonald and Schulz, 2009). It appears that multiple genetic and environmental factors operate together to push individuals over a threshold into expressing the characteristic clinical picture (Tsuang et al., 2004; Di Forti et al., 2007a).

One environmental factor which has been curiously neglected is the evidence that certain drugs can contribute to the onset of schizophrenia-like psychosis. Since the mid-twentieth century, more knowledge has accumulated concerning this than any other causal factor. Here, therefore, we examine the evidence that acute administration of drugs such as lysergic acid diethylamide (LSD), amphetamines, phencyclidine (PCP), and cannabis can induce psychotic symptoms, and consider the implications for our understanding of schizophrenia.

However, before we discuss these issues it is appropriate to remind ourselves of a few definitions. The clinical definition of a *psychotic* disorder restricts the term to those illnesses with delusions and/or prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature (DSM-IV). A drug with *psychotomimetic* actions is one which induces temporary states of altered perception (McGraw-Hill, 1993), often mimicking the symptoms of psychosis, including delusions, and/or hallucinations (“psychoto-” from psychosis, and “-mimetic” from the Greek μιμητις ὅς “in imitation of”). Thus, experimental studies examine those effects of drugs that resemble the positive symptoms (e.g., hallucinations, delusions, paranoia, and disorganized thinking) and

negative symptoms (affective flattening, anhedonia, amotivation, attentional impairment, and cognitive impairment) of schizophrenia (D’Souza et al., 2004).

## LSD AND THE SEROTONIN HYPOTHESIS

The first drug to attract major attention as a possible model of psychosis was LSD. LSD was synthesized in 1938 by Hofmann (1980), but its hallucinogenic properties were not discovered till Hofmann accidentally spilt some on his skin 5 years later, when he recalled later “I happened to experience its unforeseeable effects in my own body – or rather, in my own mind,” seeing uninterrupted streams of “fantastic pictures, extraordinary shapes with intense kaleidoscopic play of colors”.

In the 1960s, the use of LSD and other recreational drugs spread among young people across the Western world. Timothy Leary, an advocate of psychedelic drugs, was fired from Harvard University, where he was a lecturer from 1959 to 1963, and founded the League for Spiritual Discovery (L.S.D.). His phrase “Turn on, tune in, drop out!” became an anthem of the hippie movement. More serious individuals such as the famous author, Aldous Huxley also advocated the use of LSD “to make this trivial world sublime,” and even took the drug on his deathbed.

Neuropharmacologists began to ask whether schizophrenia might be caused by chemical alterations similar to those produced by LSD. Shaw and Woolley (1956) hypothesized that LSD might act on 5-HT receptors, and later Anden et al. (1968) suggested a direct agonist effect at 5-HT receptors in the CNS. The idea that the psychotic state induced by LSD resulted from actions at serotonin receptors led to the suggestion that LSD provides a “model psychosis” and to the serotonin hypothesis of schizophrenia.

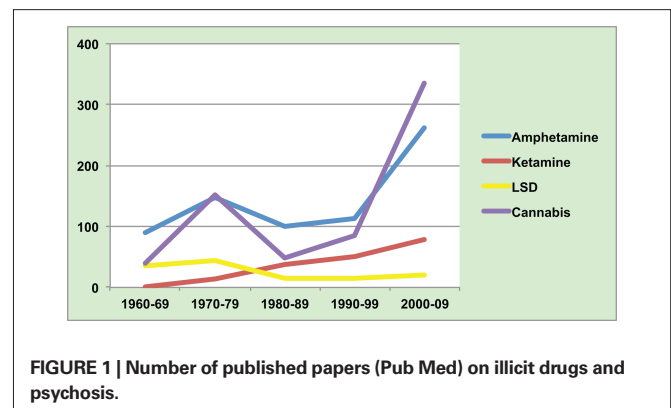
One consequence was a great deal of interest in other hallucinogens such as *N,N*-dimethyltryptamine (DMT; Manske, 1931), an endogenous substance suspected of being synthesized by the pineal gland (Rodriguez, 2007). Szara (1956) gave DMT to healthy volunteers and reported hallucinations, distortions of perception and body image, speech disturbances, and euphoria. The idea arose that schizophrenia might be caused by endogenous hallucinogens, and differences in levels of DMT in urine and blood between schizophrenic patients and controls were reported (Franzen and Gross, 1965; Gillin et al., 1976). Narasimhachari et al. (1972) gave an MAO inhibitor (tranylcypromine) and cysteine to both groups and found an exacerbation of symptoms and an increase in urinary DMT only in schizophrenics. In 1979 one of us (RMM), studying the excretion of DMT and its precursor *N*-methyltryptamine (NMT), found a greater DMT excretion in cases of schizophrenia compared to controls (Murray et al., 1979); the reasons for these differences were never established (Strassman, 1991).

Glennon et al. (1983) proposed the 5-HT<sub>2</sub> receptor subtypes as the specific target of hallucinogenic drugs such as LSD. Subsequent studies in rodents supported this (Nichols, 2004), and investigations in healthy volunteers provided evidence of 5-HT<sub>2A</sub> receptor mediation in producing psychotomimetic effects in humans (Vollenweider et al., 1998; Carter et al., 2007). The serotonin hypothesis received further support from the finding of 5-HT<sub>2</sub>-receptor abnormalities in post-mortem schizophrenic brains (Mita et al., 1986; Gurevich and Joyce, 1997), but *in vivo* studies of 5-HT<sub>2</sub>-receptor abnormalities reported conflicting results. Recently, Rasmussen et al. (2010) assessed 30 antipsychotic-naïve schizophrenic patients and matched healthy controls, finding that the patients had lower serotonin 2A binding in the frontal cortex. Positron emission tomography (PET) scanning in humans showed that hallucinogens as psilocybin produced a marked activation of the pre-frontal cortex caused by serotonergic (Arora and Meltzer, 1991; Joyce et al., 1993; Vollenweider et al., 1997). The evidence that clozapine is particularly efficacious in the care of treatment resistant schizophrenia provoked further interest because of the 5-HT<sub>2</sub> receptor antagonism induced by this drug and other atypical antipsychotics (Lieberman et al., 1998; Meltzer, 1999; Tamminga and Holcomb, 2005).

Breakey et al. (1974) who investigated the relationship between LSD use and the age of onset of schizophrenia commented "On the basis of these results it seems plausible to conclude that the taking of drugs might play some precipitating role in the onset of schizophrenia, bringing this disorder on more quickly." This statement has been amply confirmed. Vardy and Kay (1983), comparing patients hospitalized for LSD psychosis with first-break schizophrenics, suggested that LSD psychosis was a drug-induced schizophreniform reaction; moreover they concluded that there was a greater psychotic response to LSD in persons with genetic predisposition to schizophrenia.

### AMPHETAMINE, CRYSTAL METH, AND THE DOPAMINE THEORY

As seen in Figure 1, the heyday of research into LSD and other hallucinogens was in the 1960s. However, new laws restricted researchers' ability to study these drugs, and it became clear that LSD produced a psychosis with more visual and fewer auditory aberrations than is typical of schizophrenia. Interest switched to amphetamines.



**FIGURE 1 |** Number of published papers (Pub Med) on illicit drugs and psychosis.

The similarity of amphetamine psychosis to schizophrenia was first clearly described in the 1950s by Tatetsu et al. (1956) and was substantiated by a similar report in Britain from Connell (1958). Subsequently, Angrist et al. (1974) found that amphetamine administered experimentally produced a picture similar to paranoid psychosis in healthy individuals and exacerbated psychotic symptoms in approximately one-third of schizophrenic patients (Lieberman et al., 1987); moreover neuroleptic drugs blocked these psychotogenic effects of amphetamines (Espelin and Done, 1968). Amphetamine was found to stimulate dopamine outflow, while, in contrast, antipsychotics were found to block dopamine receptors in the brain (Carlsson and Lindqvist, 1963; Van Rossum, 1967). Subsequently SPET and PET studies demonstrated that acute administration of amphetamine induced greater striatal dopamine release in first-episode schizophrenia patients compared to healthy controls (Laruelle et al., 1996; Breier et al., 1997). Together these observations provided the basis for the dopamine hypothesis of schizophrenia (Snyder, 1972).

Since the 1990s there has been a marked increase in use of methamphetamine (sometimes termed crystal meths) particularly in South-East Asia [United Nations Office on Drugs Crime (UNODC), 2009], producing a rapid rise in methamphetamine psychosis in the same countries (Chen et al., 2003). In 2003 Chen and colleagues recruited 445 amphetamine users from a psychiatric hospital and a detention center in Taiwan. One hundred sixty-three had methamphetamine psychosis which presented a picture almost identical to that of paranoid schizophrenia. In most cases the symptoms slowly disappeared following cessation of the drug but in a proportion they did not remit readily, if ever (Grelotti et al., 2010). Chen and colleagues subsequently addressed the question of why some methamphetamine users became psychotic while others appeared to be able to continue their use without major problems. Not surprisingly, earlier and greater use of methamphetamine was associated with increased risk of psychosis. More interestingly, methamphetamine users with a pre-existing psychosis-prone personality were more likely to develop frank psychosis as were those with a greater familial risk. Psychosis-prone personality and family history were also associated with a more prolonged psychotic episode (Chen et al., 2003).

Recently researchers have looked for genes that may confer a vulnerability to psychosis subsequent to methamphetamine use. Bousman et al. (2009) reviewed 38 genetic association studies, and

reported four genes associated with psychosis: DTNBP1, which codes for dystrobrevin-binding protein 1, OPRM1, which codes for the mu-opioid receptor, SNCA, implicated in the modulation of dopamine transmission, and a single haplotype of SOD2, which encodes a mitochondrial protein important in cellular defense against oxidative damage. It remains to be seen how robust these associations are.

Generally speaking, amphetamine, and methamphetamine do not produce a psychosis after initial use but after repeated use. An appropriate theory has to explain this and also why abstinent methamphetamine abusers can be precipitated back into a psychosis not only by further methamphetamine abuse but also by social stress. One possibility is dopamine sensitization (Ljebberman et al., 1990; Glenthøj and Hemmingsen, 1997). In rodents, repeated administration of amphetamine leads to reversed tolerance and an increased neurochemical and behavioral reaction to each dose. Boileau and colleagues tested whether this might happen also in humans. They administered dextroamphetamine by mouth on days 1, 3, and 5 to 10 healthy volunteers, and measured the effect on striatal dopamine release before exposure, then the day of first exposure, then 2 weeks later after the third dose, using the PET/[11C] raclopride technique. Each dose of amphetamine caused greater dopamine release in the ventral striatum together with greater behavioral responses. Indeed, 1 year later there was a greater psychomotor response and greater increase dopamine release compared to the initial dose, in the ventral striatum, progressively extending to the dorsal caudate and putamen (Boileau et al., 2006). Such findings have led to the “dopamine sensitization” hypothesis of schizophrenia which postulates that a sensitized dopamine system is responsible for the genesis of psychotic symptoms (Peleg-Raibstein et al., 2009).

Prolonged methamphetamine abuse may produce permanent damage to neurons. Thus, a PET study showed a reduction in dopamine transporter density in methamphetamine users, which seemed to be related to the duration of methamphetamine use, and to the chronic psychotic state in methamphetamine users (Iyo et al., 2004).

### ANGEL DUST PROVOKES THE GLUTAMATE THEORY

The “dopamine theory” of schizophrenia has dominated attempts to explain the positive symptoms seen in schizophrenic patients (Kapur and Mamo, 2003) but is less able to account for negative symptoms. Drugs acting on the glutamate system have been proposed to model these. Kotz and Merkel (1926) discovered the compound, 1-piperidinocyclohexanecarbonitrile, and thus laid the groundwork for the preparation of PCP which was developed as an intravenous general anesthetic in the 1940s by Parke, Davis & Co. Unfortunately, up to 50% of adult patients given PCP developed agitation and hallucinations (Greifenstein et al., 1958; Johnstone et al., 1958; Collins et al., 1960), so the focus of investigation of PCP shifted from its possible use as an anesthetic to its capacity to produce model psychoses (Luby et al., 1962). Acute administration of PCP to healthy volunteers produced severe disturbances in body image, affect and thinking with impressive similarity to “certain primary symptoms of the schizophrenic process” (Luby et al., 1959); as well as severe impairments of attention, motor function, and proprioceptive

acuity (Rosenbaum et al., 1959). Although PCP was removed from clinical use in 1965, it became popular as a recreational drug as “angel dust.”

Subsequently, ketamine, another glutamate antagonist was introduced as an anesthetic, and later reports of ketamine induced psychosis started to appear. In 1983 Anis and colleagues showed that ketamine and phencyclidine selectively reduce responses of central neurons acting at the *N*-methyl-D-aspartate (NMDA) receptor (Anis et al., 1983; Seeman and Tellerico, 2005). The observation that PCP and ketamine are NMDA antagonists together with the findings of lower levels of glutamate (by about 50%) in cerebrospinal fluid samples from schizophrenic patients compared to controls gave rise to the “glutamate hypothesis of schizophrenia” (Kim et al., 1980). Although, this latter finding was not consistently replicated, the idea of hypoglutamatergic transmission in schizophrenia has continued to attract great interest as has the effects of NMDA antagonists (Tamminga and Holcomb, 2005). A dissenting view comes from Pomeroy and colleagues who gave ketamine to 10 healthy volunteers. The commonest feature was referential thinking of a delusional nature, together with a range of perceptual abnormalities perhaps best described as dissociative. However, it did not induce hallucinations, and the authors were doubtful about its ability to cause thought disorder; furthermore, although negative-like symptoms resulted they could not exclude the possibility that this was simply due to its anesthetic effects (Pomarol-Clotet et al., 2006).

According to the glutamate deficiency theory, drugs which enhance glutamate neurotransmission should improve psychotic symptoms. Trials of glutamate potentiation using glycine and related compounds have not reported any antipsychotic effects (Deakin and Simpson, 1997) but in 2007 Lilly developed LY2140023 which is a pro-drug of LY404039, a selective agonist for metabotropic glutamate 2/3 (mGlu2/3) receptors. A randomized, three-armed, double-blind, placebo-controlled study showed that schizophrenic patients treated with LY2140023 improved to a similar extent to those treated with olanzapine, both showing greater improvement on the positive and negative syndrome scale (PANSS) than placebo (Patil et al., 2007). The precise mechanism by which this drug acts on schizophrenia is not yet fully understood. However, mGluR2/3 agonists have been shown to inhibit dopamine release leading to the suggestion that dopamine abnormalities in psychosis could be secondary to a primary hypofunction in glutamate neurotransmission (Snyder and Murphy, 2008). Seeman and Tellerico (2005) set out to test this last hypothesis, and found that phencyclidine and ketamine act on the high affinity state of dopamine D2 receptors (dissociation constants of 3 and 55 nM, respectively) suggesting a direct or indirect dopamine-mimetic action of phencyclidine.

### CANNABIS: THE SACRED AND UBIQUITOUS HERB

Cannabis is the world’s favorite illicit recreational drug. Its use grew in many countries in the latter part of the twentieth century and now more than 160 million people take it every day. Within Western Europe there have been marked variations in its use (**Figure 2**) with some countries showing a recent decline in the drug’s popularity, e.g., UK, while in others its use continues to grow, e.g., Italy [European Monitoring Centre for Drugs, and Drug Addiction Annual Report, 2009].

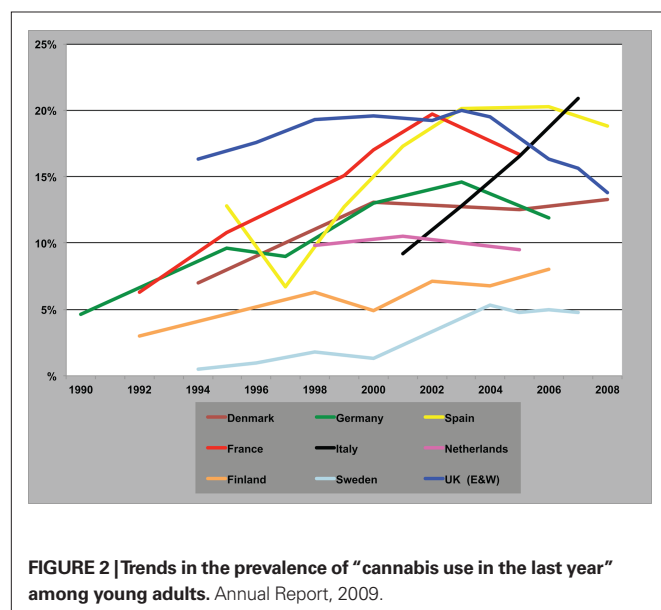
Cannabis has been linked to the development of psychotic symptoms since time immemorial. The world's oldest pharmacopeia, the *Pen-Ts'ao Chin*, traditionally attributed to the Chinese Emperor Shen Nung (2737 a.c.), suggests cannabis use as a remedy for rheumatic pain, intestinal constipation, disorders of the female reproductive system, and malaria, but adds that "if taken in excess will produce visions of devils ... over a long term, it makes one communicate with spirits and lightens one's body..." (Zuardi, 2006). In the mid-nineteenth century the French psychiatrist Moreau de Tour noted the phenomenological similarities between drug-induced states and psychosis. Indeed, he proposed the use of hashish to study madness a full century before the LSD model of psychosis (Beringer, 1927; Hofmann, 1980).

The first convincing evidence that cannabis might be a risk factor for psychosis came from the Swedish Conscripts Study on in which 45,570 inductees into the military were followed-up for 15 years. This

study reported a risk for schizophrenia 2.4 times higher among those who had used cannabis by 18 years than among non-users. Moreover, there was a dose-response relationship in that risk for schizophrenia rose to 6.0 times in heavy cannabis smokers (use of cannabis more than 50 times at initial interview; Andreasson et al., 1987). After 15 years of silence, other epidemiological studies on cannabis use and schizophrenia started to be published (Arseneault et al., 2002; Van Os et al., 2002; Zammit et al., 2002; Fergusson et al., 2003). As summarized in **Table 1**, today consistent evidence supports an association between heavy cannabis use and the risk of psychotic symptoms and illness (Green et al., 2005; Henquet et al., 2005; Fergusson et al., 2006; Barnett et al., 2007; Di Forti et al., 2007b; Moore et al., 2007; Mc Grath et al., 2010) even if the strength and nature of that association is still an object of discussion (D'Souza et al., 2004).

Recent meta-analyses reported an increase of the risk between 1.4 and 1.9 times in people using cannabis that might account for 8–14% of cases of schizophrenia in different countries (Moore et al., 2007). Furthermore, Di Forti et al. (2009) showed a positive association between the potency and frequency of cannabis use in increasing the risk of psychotic illness.

Delta-9-tetrahydrocannabinol (THC) is the main psychoactive ingredient in cannabis; when given experimentally in sufficient dosage, it can produce transient psychotic symptoms and impaired memory via stimulation of CB1 receptors, targets for the endogenous cannabinoid [*endocannabinoid* (eCB)] transmitters (Matsuda et al., 1990; Freund et al., 2003; Zuurman et al., 2010). Several studies have shown that either pure THC or synthetic CB<sub>1</sub> agonists elicit psychotic symptoms in a proportion of healthy volunteers (Leweke et al., 1999a,b; D'Souza et al., 2004; Morrison et al., 2009; Zuurman et al., 2009). CB1 receptors are widely distributed throughout the central nervous system, particularly in the hippocampus, amygdala, cerebellum, basal ganglia, and pre-frontal cortex (Herkenham et al., 1991). They are primarily expressed on glutamate and GABA-ergic terminals (Freund et al., 2003; Chevalyre et al., 2006), and upon stimulation by cannabinoids, act to reduce pre-synaptic glutamate or GABA release (Chevalyre et al., 2006). The glutamate and GABA inputs to the band of dopamine neurons



**Table 1 | Studies suggesting an association between cannabis use and psychosis.**

Study	N	Design	Prevalence/use of cannabis	Outcome	Adjusted risk
Andreasson et al. (1987)	45,570	Longitudinal conscript cohort (Sweden)	>50 times	Hospitalization	2.3
Arseneault et al. (2002)	759	Prospective birth cohort (Dunedin)	Lifetime	Any schizophreniform Disorders	3.1
Van Os et al. (2002)	4095	Longitudinal population-based (Netherlands)	Lifetime	Any psychotic symptom	2.8
Fergusson et al. (2003)	1011	Birth cohort (Christchurch)	DSM-IV dependence	Any psychotic symptom	1.8
Zammit et al. (2002)	50,087	Longitudinal conscript cohort (Sweden)	>50 times	Hospitalization	3.1
Henquet et al. (2005)	3467	Prospective cohort (Germany)	Lifetime	Any psychotic symptom	1.7
Di Forti et al. (2009)	280	Case-control (UK)	Lifetime	First-episode psychosis	6.8 (skunk users)
Mc Grath et al. (2010)	3801	Prospective cohort (Australia)	≥6 years duration	Non-affective psychosis	2.1



in the ventral midbrain express CB<sub>1</sub> receptors and numerous animal studies have shown that exogenous cannabinoids alter the balance of excitation and inhibition reaching dopamine cells (Lupica and Riegel, 2005; Matyas et al., 2008). Although a net inhibition of dopamine cells has been described (Melis et al., 2004), by far the most commonly documented effect is an increase in firing with attendant elevations of dopamine release at downstream forebrain territories (Lupica and Riegel, 2005).

One testable hypothesis which arises is whether the psychotomimetic properties of THC in humans are mediated via excess dopamine release. Bossong et al. (2009) used a dopamine D<sub>2</sub>/D<sub>3</sub> receptor tracer (raclopride) and positron emission tomography, to examine striatal synaptic dopamine release. The tracer binding was significantly reduced in the ventral striatum and the precommissural dorsal putamen after inhalation of THC compared to placebo, implying an increased release of endogenous dopamine in these regions. However, the increase is modest compared to that obtained with amphetamine and cocaine, and two other studies have failed to find such clear-cut results (Stokes et al., 2009). For example, another PET study by Stokes et al. (2009) found only a non-significant increase in dopamine release in the striatum following oral THC. Later Stokes et al. (2010) re-analyzed their initial data and showed significant decreases in cortical [11C]-raclopride binding potential after administration of THC, suggesting dopamine release in the cortex. Our own group observed clear psychotic phenomena (including thought-echo and passivity) in a group of 10 healthy volunteers given IV THC during SPET scanning but there were no significant differences in DA release between THC and placebo sessions, nor were positive symptoms and DA release related (Barkus et al., 2010). Furthermore, D'Souza et al. (2005, 2008) showed that D2 blockers did not offer "protection" against acute THC-psychosis, either in healthy controls or in stable schizophrenic patients. However, the validity of this interpretation needs to be investigated and whether the psychotomimetic properties of THC arise by way of downstream dopaminergic events is currently unclear.

Indeed, the reverse may be true. One of the downstream effects of stimulating D2 receptors in the striatum is the synthesis and release of endocannabinoid transmitters (Giuffrida et al., 1999; Centonze et al., 2004; Kreitzer and Malenka, 2005; Yin and Lovinger, 2006; D'Souza et al., 2008; Stokes et al., 2010) at the dendritic spines of medium spiny neurons (MSNs; Uchigashima et al., 2007). In turn, eCBs act in a so-called retrograde fashion to inhibit neighboring GABA and glutamate terminals (Gerdeman et al., 2002; Robbe et al., 2002; Freiman et al., 2006; Adermark et al., 2009). There is accumulating evidence that a number of key physiological processes within the striatum depend upon D2 → eCB → CB<sub>1</sub> signaling and the subsequent modification of fast amino-acid based transmission (Calabresi et al., 2007; Kreitzer and Malenka, 2008). Such processes are believed to be vital for the selection and initiation of psychomotor behaviors and for associative learning, or in other words, the normal functions of the striatum in health (Graybiel, 2005; Yin and Knowlton, 2006; Houk et al., 2007; Kreitzer and Malenka, 2007). One question which arises is whether the pro-psychotic effects of not just THC, but stimulant drugs as well involve the striatal D2 → eCB → CB<sub>1</sub> trans-synaptic pathway. If this were the case then it might explain why D2 blockade has little effect on THC-psychosis

because THC "enters" the pathway at a point which is distal to D2 receptors. In contrast pharmacological manipulations at CB<sub>1</sub> would be predicted to impact upon stimulant (D2 initiated), psychosis, since CB<sub>1</sub> is downstream of D2. Several lines of evidence suggest that this might be the case.

It is clear that stimulant sensitization or adaptations to repeated drug administration as opposed to single drug exposures, are important for the emergence of psychosis. One of the outcomes of repeated stimulant administration is a functional up-regulation of striatal CB<sub>1</sub> receptors (Centonze et al., 2007). Furthermore, several recent studies have shown that either CB<sub>1</sub> knockout or blockade of CB<sub>1</sub> receptors by potent CB<sub>1</sub> antagonists impairs stimulant sensitization (Corbille et al., 2007; Thiemann et al., 2008a,b). In a particularly elegant design it was demonstrated that microinjections of a potent CB<sub>1</sub> antagonist directly into the ventral striatum reduced the expression of behavioral sensitization to methamphetamine (Chiang and Chen, 2007). Findings with the first generation CB<sub>1</sub> blocker rimonabant in sensitization paradigms have been inconsistent (Lesscher et al., 2005; Thiemann et al., 2008b), but rimonabant, as opposed to newer CB<sub>1</sub> antagonists, only partially blocks the effects of THC in humans (Huestis et al., 2001; Zuurman et al., 2010) which might explain why an early trial of rimonabant in schizophrenia failed (Meltzer et al., 2004). Rimonabant is also ineffective in animal models of cocaine reward, in contrast to CB<sub>1</sub> antagonists such as AM251 (Gardiner, personal communication).

Another cannabinoid manipulation has shown more promise. The molecule cannabidiol (CBD), a constituent of free-growing, natural *Cannabis sativa* (but largely eliminated from high potency cannabis preparations such as skunk; Potter et al., 2008) appears to have antipsychotic properties in humans (Leweke et al., 2000; Zuardi et al., 2009). At low doses, the receptor pharmacology of CBD involves pharmacological antagonism of CB<sub>1</sub> agonists (despite low affinity for the orthosteric site of CB<sub>1</sub> receptors) and inhibition of adenosine re-uptake. CBD also inhibits the degradation of the endocannabinoid molecule anandamide and acts at a "third" cannabis receptor termed GPR55 (Pertwee, 2007). CBD displays efficacy against stimulant (Zuardi et al., 1991; Moreira and Guimaraes, 2005) and NMDA models of psychosis in animals (Long et al., 2006), and against L-DOPA (Zuardi et al., 2009), ketamine (Bosi et al., 2003), and THC elicited psychosis in humans (Zuardi et al., 1982; Bhattacharyya et al., 2009). A single head-to-head trial of CBD vs amisulpride in 42 schizophrenic patients found equivalent efficacy (Leweke, 2007), but further data, particularly over the longer term, is required before we can definitely conclude that these antipsychotic effects are real.

Overall, the above suggests a model in which pharmacological manipulations to neurochemical systems controlling traffic through striatal circuits can be either pro- or antipsychotic. The most notable feature is the consistency of the pharmacology with which facilitating the D2 → eCB → CB<sub>1</sub> axis appears to be pro-psychotic.

## CONCLUSION

We have seen that a great deal of knowledge has accumulated concerning drug-induced psychoses over the last 50 years. However, the picture presenting in the clinic, as opposed to that seen in the experimental setting, has not been widely acknowledged as telling

us much about schizophrenia itself. Perhaps the main reason for this is that when drug-induced psychoses were first identified, schizophrenia was considered a discrete disease with a likely single genetic cause. Consequently, drug-induced psychoses, even those phenomenologically very similar to schizophrenia, were seen as phenocopies rather than examples of the schizophrenia syndrome consequent upon the operation of a particular cause. However, now that schizophrenia is generally viewed as at the extreme end of a continuum of psychosis where the combined effect of genetic and environmental factors pushes the individual over a threshold into the expression of the disorder. In the light of this new knowledge it is time to re-appraise the drug-induced psychoses.

Certainly the major pharmacological theories of schizophrenia have their origins in the effects of drugs of abuse; in chronological order, the effects of LSD initiated the serotonergic model; amphetamines the dopamine hypothesis, PCP, and ketamine the glutamatergic model. Most recently the effects of cannabis have provoked interest in the role of endocannabinoids. None of these models account for the complete picture of schizophrenia, but this is not to be expected if we regard the condition as one with multiple causes and consequent heterogeneity of the clinical picture. Rather the various drugs mimic different aspects of the disorder. Stimulants and THC are particularly likely to induce paranoia beliefs (Javitt and Zukin, 1990), whereas LSD is more closely associated with visual illusions/hallucinations (Smith et al., 2009). The non-competitive NMDA antagonists PCP and ketamine appear to induce negative symptoms, and oneroid states (characterized by perceptual illusions, perplexity, and delusional thinking in the context of clouding of consciousness; Gonzalez-Maesó and Sealfon, 2009). What is common between the different classes of drug is the promotion of a fundamental change in the subject's experience of reality, whether acutely, during drug intoxication (in the case of LSD, ketamine, and THC) or as a result of an adaptive process secondary to repeated use (stimulants and THC).

How then is it possible to discriminate between drugs which distort the experience of reality in a way which closely corresponds to aspects of schizophrenia from those that do not? One approach is to postulate that if a drug-model pushes the CNS toward psychosis AND if it is also "true" that a diametrically opposing pharmacological manipulation pulls a schizophrenic psychosis back into reality, then the drug-model in question constitutes a reasonable model of schizophrenic-like psychosis. Some examples may illuminate this idea. Agonists at the 5HT receptor transform reality in a fundamental

way; yet 5HT<sub>2</sub> antagonists have no efficacy against schizophrenic psychosis (Zuardi, 2006). Similarly, NMDA channel blockers distort the experience of reality, yet, despite much effort and theoretical support, drugs which enhance NMDA channel opening have not yet been proven to be effective in schizophrenia.

In contrast, opposing pharmacological manipulations at D<sub>2</sub> receptors can elicit clear bi-directional responses at the psychological level. Drugs which drive D<sub>2</sub>-mediated signaling to excess have pro-psychotic properties AND D<sub>2</sub> blockers are effective against schizophrenic psychosis. On this basis, one can infer that, at a neurochemical level, the DA model psychosis is more akin to reality-distortion in schizophrenia than are either the serotonergic or glutamatergic models.

In recent years it has been suggested that excess dopamine synthesis and release in the striatum is the final, common arbiter of positive psychotic symptoms (Broome et al., 2005; Di Forti et al., 2007a; Murray et al., 2008) probably through a pathological dysfunction of the "reward" pathway (Strassman, 1984). Do all of the drugs which induce psychotic symptoms do so via their effects on the dopamine system? Certainly, as we have seen, an argument can be made that they all impact on the dopamine system either directly or indirectly. However, it is not clear that this effect accounts for their propensity to induce the characteristic positive symptoms of schizophrenia. Another caveat is that the dopamine model can probably no longer be considered in isolation from the emerging endocannabinoid model. Earlier we utilized the relatively simple concept of a D<sub>2</sub> → eCB → CB<sub>1</sub> axis to describe the known physiological relations of the two neurochemical systems within the striatum (Kreitzer and Malenka, 2008). Notably, opposing pharmacological manipulations at CB<sub>1</sub> receptors can also elicit bi-directional responses, either pro- or antipsychotic. Moreover, CB<sub>1</sub> manipulations appear to be effective against dopamine D<sub>2</sub> mediated psychoses.

Finally, not all addictive drugs which impact on the dopamine system appear to be able to induce psychotic symptoms. For example, neither cigarette smoking, nor use of opiates induce psychotic symptoms. One possible reason is that the fact that nicotine and opiate receptors (and responses) show a rapid de-sensitization following exposure to their respective agonists. This illustrates the general theme of this paper; determining the neurochemical differences between those drugs whose effects do and which do not mimic particular aspects of schizophrenia is worthy of investigation in humans as well as in animals.

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